# Loss of Glial Glutamate and Aspartate Transporter (Excitatory Amino Acid Transporter 1) Causes Locomotor Hyperactivity and Exaggerated Responses to Psychotomimetics: Rescue by Haloperidol and Metabotropic Glutamate 2/3 Agonist

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**Background:** Recent data suggest that excessive glutamatergic signaling in the prefrontal cortex may contribute to the pathophysiology of schizophrenia and that promoting presynaptic glutamate modulation via group II metabotropic glutamate 2/3 (mGlu2/3) receptor activation can exert antipsychotic efficacy. The glial glutamate and aspartate transporter (GLAST) (excitatory amino acid transporter 1 [EAAT1]) regulates extracellular glutamate levels via uptake into glia, but the consequences of GLAST dysfunction for schizophrenia are largely unknown.

**Methods:** We examined GLAST knockout mice (KO) for behaviors thought to model positive symptoms in schizophrenia (locomotor hyperactivity to novelty, exaggerated locomotor response to N-methyl-D-aspartate receptor [NMDAR] antagonism) and the ability of haloperidol and the mGlu2/3 agonist LY379268 to normalize novelty-induced hyperactivity.

**Results:** Glial glutamate and aspartate transporter KO consistently showed locomotor hyperactivity to a novel but not familiar environment, relative to wild-type (WT) mice. The locomotor hyperactivity-inducing effects of the NMDAR antagonist MK-801 was exaggerated in GLAST KO relative to WT. Treatment with haloperidol or LY379268 normalized novelty-induced locomotor hyperactivity in GLAST KO.

**Conclusions:** Schizophrenia-related abnormalities in GLAST KO raise the possibility that loss of GLAST-mediated glutamate clearance could be a pathophysiological risk factor for the disease. Our findings provide novel support for the hypothesis that glutamate dysregulation contributes to the pathophysiology of schizophrenia and for the antipsychotic potential of mGlu2/3 agonists.

**Key Words:** GLAST, glutamate, mGlu2/3, NMDA, schizophrenia

Glutamatergic dysfunction is increasingly implicated in the pathophysiology of schizophrenia (1,2). Patients with schizophrenia exhibit alterations in glutamate receptors in brain regions functionally compromised in schizophrenia, such as the hippocampus and prefrontal cortex (PFC) (3). Furthermore, treatment with N-methyl-D-aspartate receptor (NMDAR) antagonists such as ketamine and phencyclidine (PCP) mimic the symptoms of schizophrenia in healthy subjects and provoke relapse in schizophrenic patients (4,5). In rodents, NMDAR antagonists produce a range of schizophrenia-related behavioral abnormalities including locomotor hyperactivity and cognitive dysfunction (6,7). While the psychotomimetic effects of NMDAR antagonists has fostered the notion of a hypoglutamatergic state in schizophrenia, recent data suggest that these effects stem from PFC glutamate excess caused by disinhibition of NMDAR-containing gamma-aminobutyric acid (GABA)ergic interneurons (8–13). In support of this hypothesis is preliminary evidence of antipsychotic efficacy of group II metabotropic glutamate 2/3 (mGlu2/3) agonists (14) that negatively modulate glutamate in PFC (15).

These developments raise the possibility that molecular abnormalities leading to PFC glutamate excess could be risk factors for schizophrenia. Glial glutamate and aspartate transporter (GLAST) (excitatory amino acid transporter 1 [EAAT1]), glial glutamate transporter-1 (GLT-1) (excitatory amino acid transporter 2 [EAAT2]), excitatory amino-acid carrier 1 (EAAC1) (excitatory amino acid transporter 3 [EAAT3]), and excitatory amino acid transporter 4 (EAAT4) belong to a family of sodium-dependent glutamate transporters that tightly regulate extracellular concentrations (16,17). Glial glutamate and aspartate transporter is mainly expressed in astrocytes within the rodent cerebellum but is also found, albeit in lesser concentrations, in hippocampus, cerebral cortex, and thalamus (16,17). Antisense knockdown of GLAST has been shown to cause increased levels of extracellular glutamate concentrations in hippocampus and striatum and increased vulnerability to glutamatergic toxicity (18). Intriguingly, genetic mutation of human GLAST (*SLC1A3*) was recently linked to schizophrenia (19). However, the consequences of disrupted GLAST function for schizophrenia-related behavioral phenotypes have not been studied, in part due to a lack of GLAST-specific pharmacological tools.

Here, we tested a GLAST knockout (KO) model (20) for phenotypes considered relevant to the positive symptoms of schizophrenia (locomotor hyperactivity to novelty, hypersensitivity to NMDAR antagonists) (6,7). We then tested whether the novelty-induced hyperlocomotor phenotype was reversible with a typical antipsychotic (haloperidol) and an mGlu2/3 agonist (LY379268).

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## Methods and Materials

### Subjects

Glial glutamate and aspartate transporter KO were generated as previously described (20) (Supplement 1). Experimental procedures were approved by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Animal Care and Use Committee and followed the National Institutes of Health (NIH) guidelines, "Using Animals in Intramural Research."

### Locomotor Activity in Novel and Familiar Environment

Locomotor responses were tested in a novel square arena (40 × 40 × 35 cm, 55 lux) constructed of white Plexiglas as previously described (21). Distance traveled and time spent in the center (20 × 20 cm) were measured over 60 min via Ethovision (Noldus Information Technology Inc., Leesburg, Virginia).

Locomotor activity in a familiar environment was assessed over 24 hours (after 48 hours acclimation) in individual home cages under normal vivarium conditions via the photocell-based Opto M3 activity monitor (Columbus Instruments, Columbus, Ohio) (21).

### Locomotor Response to MK-801

To circumvent basal hyperactivity to novelty in GLAST KO confounding assessment of the hyperactivity-inducing effects of MK-801, mice tested for the response to novel stimulus (above) were re-exposed to the open field and acclimated for a further 60 min. Mice were then injected with .2 mg/kg MK-801 and returned to the open field for 60 min (further details in Supplement 1).

### Locomotor Effects of Haloperidol and mGlu2/3 Agonist LY379268

Open field naïve mice were injected intraperitoneal (IP) with vehicle or .3 mg/kg haloperidol and tested in the open field for 30 min as above.

Before testing the effects of LY379268 in GLAST KO, we first established doses sufficient to normalize phencyclidine-induced locomotor activity in nonmutant male C57BL/6J mice. Mice were injected with saline or .3, 1.0, or 3.0 mg/kg LY379268 and 30 min later, were placed in the open field. After 60 min of acclimation, mice were injected with 5.0 mg/kg phencyclidine and tested in the open field for 60 min as above.

On the basis of the C57BL/6J dose-response data (Supplement 2), open field naïve GLAST KO were injected with vehicle or 1.0 mg/kg LY379268 and 30 min later tested in the open field for 30 min as above.

### Statistical Analysis

Data were analyzed using Statistica (Statsoft, Tulsa, Oklahoma). Effects of genotype, sex, drug treatment, and time were analyzed using analysis of variance (ANOVA) (repeated measures for time) followed by Tukey post hoc tests.

## Results

### Locomotor Activity in Novel and Familiar Environment

In the novel open field, there was a significant main effect of genotype [$F(2,45) = 10.58$, $p < .01$] and time [$F(11,495) = 2.00$, $p < .05$] but no genotype × time interaction for distance traveled (Figure 1A). Post hoc analysis revealed that KO were significantly more active than wild-type (WT) during novel open field exposure. We also noted a significant main effect of sex [$F(1,45) = 4.70$, $p < .05$] and significant genotype × sex interaction [$F(2,45) = 3.39$, $p < .05$] for distance traveled and therefore further analyzed locomotor activity separately within each sex. This confirmed a robust and significant effect of genotype in both male [$F(2,22) = 6.70$, $p < .01$] and female mice [$F(2,23) = 7.18$, $p < .01$], with a more pronounced difference between female KO and WT than between male KO and WT underlying the interaction effect in the global analysis. Time spent in the center of open field, a putative measure of anxiety-like behavior, was unaffected by genotype or sex (Figure 1B). There was no significant effect of genotype, sex, or genotype × sex interaction for locomotor activity in the familiar home cage (Figure 1C). Two mice were removed from the home cage test due to scores higher than two standard deviations (SD) above mean (SD = 209695).

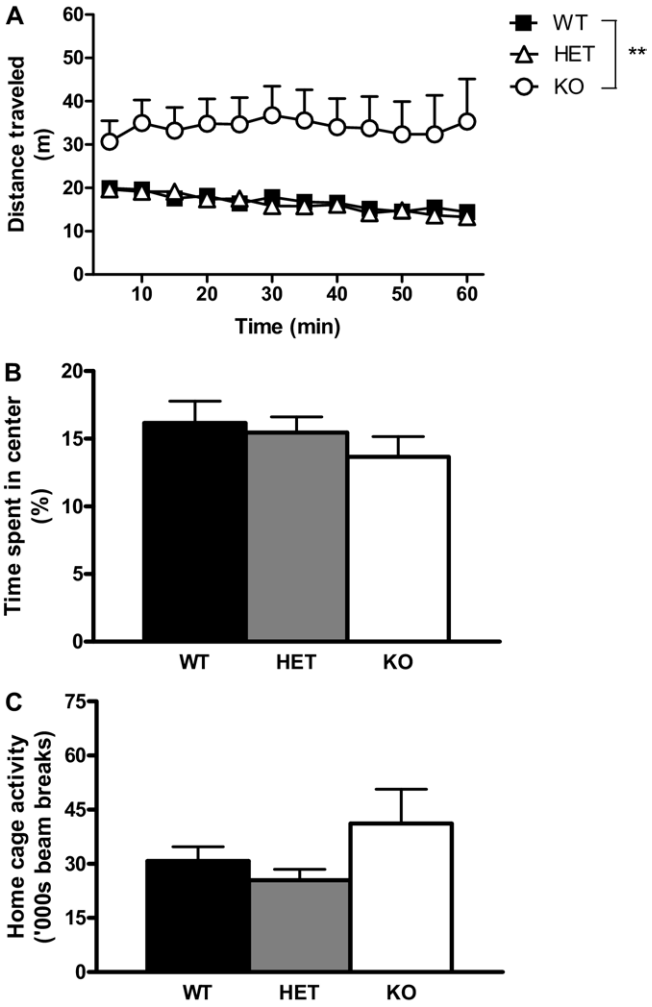


**Figure 1.** Locomotor hyperactivity in response to environmental novelty in GLAST KO. **(A)** GLAST KO showed elevated locomotor activity than WT during exposure to a novel open field ($n = 14–20$). **(B)** Time spent in the center of the open field did not differ between genotypes. **(C)** Home cage locomotor activity was no different between genotypes ($n = 13–16$). $^{**}p < .01$. Data are mean ± SEM. GLAST, glial glutamate and aspartate transporter; HET, heterozygous; KO, knockout; WT, wild-type.

### Locomotor Response to MK-801

Analyzing predrug time block, there was a main effect of time [$F(11,242) = 19.85$, $p < .01$], reflecting some residual habituation in all genotype groups, but no main effect of genotype or genotype × time interaction. The lack of genotype effect,

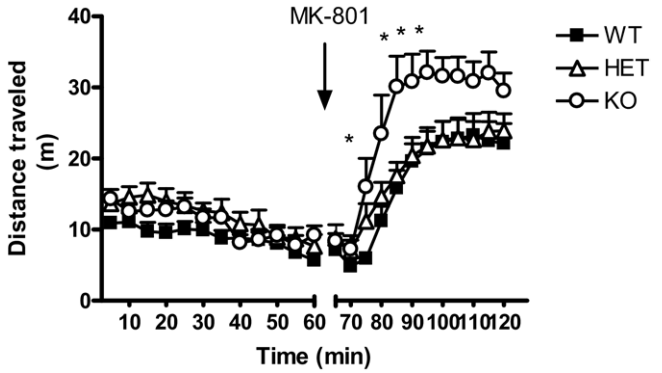


**Figure 2.** Increased sensitivity to the locomotor hyperactivity-inducing effects of MK-801 in GLAST KO. Treatment with .2 mg/kg MK-801 produced a significantly greater increase in open field locomotor activity in GLAST KO than WT ($n = 9–10$). *$p < .05$ versus WT. Data are mean ± SEM. GLAST, glial glutamate and aspartate transporter; HET, heterozygous; KO, knockout; WT, wild-type.

together with the lower overall activity levels compared with the novel open field, shows that hyperactivity in GLAST KOs is selectively found under conditions of novelty.

The response to MK-801 challenge was subsequently evaluated using mixed-model ANOVA for postinjection time points and controlling for individual differences in baseline as covariates using the last 15 min of predrug baseline. There was a significant effect of genotype [$F(2,21) = 4.21$, $p < .05$], time [$F(5,105) = 2.57$, $p < .05$], and a genotype × time interaction [$F(22,231) = 1.87$, $p < .05$] for total distance traveled. Post hoc analysis showed that MK-801 increased activity in KO to a greater extent than WT (Figure 2). There was also significant effect of sex [$F(2,21) = 6.88$, $p < .05$] and a sex × time interaction [$F(11,231) = 1.99$, $p < .05$] due to female mice responding to MK-801 challenge more profoundly than male mice. Sex did not significantly influence the genotypic differences in responsivity to MK-801, as shown by a lack of genotype × sex or genotype × sex × time interactions.

### Locomotor Effects of Haloperidol in GLAST KO Mice

For the haloperidol rescue test, there was a significant main effect of genotype [$F(2,62) = 5.00$, $p < .01$] and drug [$F(1,62) = 30.93$, $p < .01$] and a significant genotype × drug interaction [$F(2,62) = 5.97$, $p < .01$] for total distance traveled. Post hoc tests showed that KO were more active than WT following vehicle treatment but not following haloperidol treatment (Figure 3A). Haloperidol significantly reduced locomotor activity in heterozygous (HET) and KO but not WT. There was an overall effect of sex [$F(1,62) = 4.29$, $p <. 05$] due to higher scores in female mice than male mice (post hoc test: $p <. 01$) but sex did not interact with either drug or genotype.

### Reversal of PCP-Induced Hyperlocomotion by the mGlu2/3 Agonist LY379268 in C57BL/6J Mice

There was an overall significant effect of treatment [$F(3,32) = 11.08$, $p < .01$], time [$F(3,32) = 27.88$, $p < .01$], and a time × drug interaction for total distance traveled [$F(69,736) = 3.76$, $p < .01$]. Analyzing pre-PCP, there was a significant effect of treatment [$F(3,32) = 4.58$, $p < .01$] and time [$F(11,352) = 32.94$, $p < .01$] but no treatment × time interaction. Post hoc tests showed that prior to the PCP challenge, 3.0 but not .3 or 1.0 mg/kg LY379268 significantly decreased activity relative to vehicle (Supplement 2).

The response to PCP challenge was evaluated using mixed-model ANOVA for postinjection time points and controlling for individual differences in baseline as covariates using the last 15 min of predrug baseline. There was a significant effect of treatment [$F(3,31) = 11.64$, $p < .01$] but no time or treatment × time interaction effect. Post hoc test showed that 1.0 and 3.0 mg/kg LY379268 prevented PCP-induced hyperactivity relative to vehicle (Supplement 2).

### Locomotor Effects of LY379268 in GLAST KO Mice

There was a significant effect of genotype [$F(2,68) = 20.29$, $p < .01$], drug [$F(1,68) = 29.33$, $p < .01$], and genotype × drug interaction [$F(2,68) = 12.31$, $p < .01$] for total distance traveled. Post hoc tests showed that KO were more active than WT following vehicle treatment but not following LY379268 treatment (Figure 3B). LY379268 significantly reduced locomotor activity in KO but not HET or WT. Because we observed a significant effect of sex [$F(1,68) = 12.77$, $p < .01$] and significant genotype × sex interaction [$F(2,68) = 13.27$, $p < .01$], we also analyzed genotype and LY379268 effects separately within each sex and found a rescue of GLAST KO hyperlocomotion in both male and female mice. Thus, in male mice, there was a significant effect of genotype [$F(2,32) = 4.76$, $p < .05$], LY379268 [$F(1,32) = 6.18$, $p < .05$], and their interaction [$F(2,32) = 4.63$, $p < .05$]. Post hoc analysis showed that KO were more active than WT after vehicle but not LY379268 treatment. Similarly, in female mice,

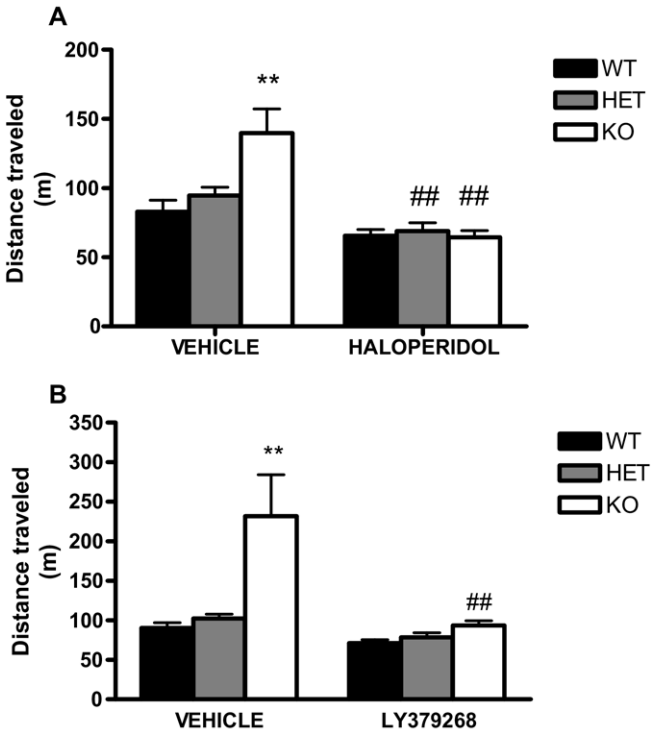


**Figure 3.** Locomotor hyperactivity in GLAST KO is rescued by haloperidol and the mGlu2/3 receptor agonist LY379268. **(A)** Treatment with .3 mg/kg haloperidol normalized novel open field locomotor hyperactivity in GLAST KO ($n = 10–14$/genotype/treatment). **(B)** Treatment with 1 mg/kg LY379268 normalized novel open field locomotor hyperactivity in GLAST KO ($n = 10–15$/genotype/treatment). *$p < .05$, **$p < .01$ versus WT/same treatment; #$p < .05$, ##$p < .01$ versus vehicle/same genotype. Data are mean ± SEM. GLAST, glial glutamate and aspartate transporter; HET, heterozygous; KO, knockout; mGlu2/3, metabotropic glutamate 2/3; WT, wild-type.

there was a significant effect of genotype [$F(2,36) = 18.51$, $p < .01$], LY379268 [$F(1,36) = 26.47$, $p < .01$], and their interaction [$F(2,36) = 9.77$, $p < .01$]. Again, post hoc tests demonstrated that KO were more active than WT after vehicle but not after LY379268 treatment.

## Discussion

The first major novel finding of the present study was that GLAST KO showed a significant and robust open field locomotor hyperactivity relative to WT. This was restricted to conditions of novelty and not seen after prior habituation to the open field (see MK-801-challenge experiment) or in the familiar environment of the home cage. Together, these data demonstrate an exaggerated GLAST KO locomotor response under conditions of sufficient environmental challenge.

The basal locomotor hyperactivity in GLAST KO phenocopies the effects of NMDAR antagonists in nonmutant mice (6,7). These drugs also aggravate symptoms in schizophrenic patients and simulate psychosis in normal subjects (4,5). Therefore, providing further support for a schizophrenia-related abnormality in GLAST KO, these mice exhibited an exaggerated locomotor hyperactivity response to the noncompetitive NMDAR antagonist MK-801. A final important observation was that basal GLAST KO locomotor hyperactivity was rescued by the prototypical antipsychotic haloperidol and the mGlu2/3 agonist LY379268 recently shown to have therapeutic efficacy in schizophrenia (14). These findings provide a pharmacological validation that reversal of GLAST KO induced hyperactivity may have predictive activity for clinical efficacy in schizophrenia and therefore provide a useful tool for screening novel antipsychotics.

Mechanistically, the ability of NMDAR antagonists to provoke human psychosis and produce schizophrenia-related behaviors in rodents has been linked to a loss of NMDAR-mediated GABAergic inhibition, leading to excessive glutamate release and neuronal hyperexcitability in PFC (8–13). Loss of GLAST is predicted to cause glutamate excess and extrasynaptic spillover under conditions that provoke glutamate release, including novelty and NMDAR-mediated GABA inhibition. Although voltametry or microdialysis measures of PFC extracellular glutamate in behaving GLAST KO would provide direct evidence of this, indirect support for this notion is given by the ability of LY379268 to rescue GLAST KO phenotype and is entirely consistent with the notion that extrasynaptic mGlu2/3 receptors facilitate inhibitory control of glutamate release and mitigate the effects of impaired clearance (22). In this context, our data offer novel support for the hypothesis that excessive glutamate contributes to the pathophysiology of schizophrenia and lend further credence to the antipsychotic potential of mGlu2/3 agonists (14).

A number of issues await clarification. First, the relative contribution of GLAST to forebrain glutamate signaling remains to be established. Glial glutamate and aspartate transporter messenger RNA and protein expression is most heavily concentrated in the cerebellum rather than the forebrain regions implicated in schizophrenia, such as the PFC and hippocampus, and neurons in these areas are not surrounded by high numbers of astrocytes where the majority of GLAST-mediated glutamate reuptake is thought to occur (16,17). Second, although acute loss of glutamate clearance provides a plausible mechanism for the schizophrenia-related abnormalities in GLAST KO, this does not exclude the potential for constitutive loss of GLAST to cause more permanent neural changes resulting from excitotoxicity (18,20) or developmental abnormalities. The neurodevelopment issue is particularly salient given that high transient GLAST gene promoter activity is present during early postnatal mouse development in both the cortex and hippocampus (23) and the posited neurodevelopmental ontogeny of schizophrenia. Third, possible GLAST KO abnormalities on behaviors pertinent to the negative and cognitive symptoms of schizophrenia await further study.

In summary, present data demonstrate that GLAST KO exhibit abnormalities on behavioral measures thought to model positive symptoms of schizophrenia. These disturbances were normalized by the prototypical antipsychotic haloperidol and the mGlu2/3 receptor agonist LY379268. Present findings suggest that loss of GLAST-mediated glutamate clearance could be a pathophysiological risk factor for schizophrenia and are particularly intriguing given recent evidence linking genetic mutation of human GLAST (*SLC1A3*) with schizophrenia (19). More generally, our data provide novel support for the hypothesis that excessive glutamate neurotransmission contributes to psychosis.

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*Supplementary material cited in this article is available online.*

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